IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Jan E. Schnitzer		
Application No.:	10/056,230	Group:	1642
Filed:	January 24, 2002	Examiner:	S.N. Ungar
Confirmation No.:	6912		
For:	TARGETING ENDOTHELIUM FOR TISSUE-SPECIFIC DELIVERY OF AGENTS		

CERTIFICATE OF MAILING

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SUBSTITUTE APPEAL BRIEF

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Sir:

This Substitute Appeal Brief is submitted in response to the Office Communication mailed from the United States Patent and Trademark Office on November 9, 2004.

I. REAL PARTY IN INTEREST

The real party in interest is Beth Israel Deaconess Medical Center, Inc., 330 Brookline Avenue, Boston, MA 02215 and Sidney Kimmel Cancer Center, 10835 Altman Row, San Diego, CA 92121. Beth Israel Deaconess Medical Center, Inc. and Sidney Kimmel Cancer Center are the Assignees of the entire right, title and interest in the subject application, by virtue of an Assignment recorded on July 26, 2002 at Reel 013127, Frames 0056-0059.

II. RELATED APPEALS AND INTERFERENCES

Appellants, the undersigned Attorney and Assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 3-5, 7-9 and 12-14 have been finally rejected. Claim1 was canceled, and Claims 2, 3, 4 and 9 were amended, in the Preliminary Amendment filed on May 27, 2003. Claims 5-8 and 10-17 appear as originally filed. Claims 2, 6, 10-11 and 15-17 have been withdrawn from consideration. A copy of the claims appears in the Appendix of this Brief

IV. STATUS OF AMENDMENTS

The Preliminary Amendment filed on May 27, 2003, has been entered. No other claim amendments have been made.

V. SUMMARY OF INVENTION

The present invention is drawn to methods of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner (independent Claim 3; see, e.g., p. 5, lines 6-13; p. 13, lines 5-9 and 11-17; p. 45, line 20, through p. 46, line 17), by targeting a component of caveolae. In particular, the claims are drawn to delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner, by selecting an agent of interest that binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface (see, e.g., p. 53, lines 8-16), wherein the component to which the agent binds and localizes is tissue specific (see, e.g., p. 13, lines 5-9; p. 39, lines 4-27; p. 40, line 28, through p. 41, line 2); and contacting the luminal surface of vasculature with the agent of interest, thereby delivering the agent into and/or across the luminal surface of the vascular endothelium in a tissue-specific manner.

In certain embodiments, the agent of interest has an active agent component and a transport agent component (Claim 4; see, e.g., p. 5, lines 6-13; p. 16, lines 29, through p. 17, line 6), in which the transport agent component binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium. In certain embodiments, the tissue can be a malignant tissue (Claim 5; see, e.g., p. 15, line 28, through p. 16, line 4; p. 16, lines 23-28). For the purposes of the restriction requirement, the elected aspects of the invention pertain to embodiments in which the agent of interest comprises a active agent component and a transport agent component which are not the same component (see, e.g., p. 5, lines 6-13; p. 16, lines 29, through p. 17, line 6); and in which the active agent component is a drug (see, e.g., p. 13, lines 5-9; p. 49, lines 13-18), the transport component is an antibody (see, e.g., p. 13, lines 1-3; p. 53, lines 8-16; [/ 39, lines 4-14), and the tissue is pulmonary (e.g., lung) (see, e.g., p. 13, lines 5-9; p. 17, lines 6-14; p. 53, lines 8-16; p. 38, lines 4-14; p. 49, lines 13-18). See also, in particular, Examples 8 (p. 35 *et seq.*) And 9 (p. 41 *et seq.*)

VI. ISSUES

The following issue remains on appeal: whether claims 3-5, 7-9, and 112-14 are not enabled under 35 U.S.C. 112, first paragraph. There are three separate subheadings under the rejection under 35 U.S.C. 112, first paragraph, set forth in paragraphs 4, 5 and 6 of the Office Action, made final. First, whether it is possible to extrapolate the teachings in the specification regarding the uptake of the combination of Mab 833/drug to the enablement of the claims; second, whether it is possible to extrapolate the teachings in the specification regarding the discovery of Mab 833 to other antibodies or agents; and third, whether the specification provided adequate written description for the scope of the claimed invention.

VII. GROUPING OF CLAIMS

Claims 3-5, 7-9 and 12-14 stand or fall together.

VIII. ARGUMENT

With regard to the first subheading of the rejection under 35 U.S.C. §112, first paragraph, the Examiner states that "given only the exemplified Mab 833 which appears to be not specific

for any therapeutic or diagnostic purpose, it is clear that the specification does not teach how to use the claimed invention for the contemplated and claimed function" (Office Action Made final, page 3). The Examiner additionally stated that the "effects of targeting the rat lung with Mab 833 are non-specific within lung" (see *id.*). This assessment is a mischaracterization of the nature of the Mab 833 and its ability to target a specific tissue and to deliver a compound to that tissue. To facilitate discussion, a brief description of the endothelium and the specific delivery of agents using Mab 833 is set forth below.

The endothelium is a single layer of thin, flattened cells that form the blood vessel wall and separates the circulating blood (including cells and molecules) and from the underlying cells inside the tissue and constituting the tissue/organ. In most organs, the endothelium acts as a significant barrier to the free passage of blood-borne molecules and cells to the underlying interstitium and tissue cells (e.g., myocardial cells of the heart tissue cells). The endothelium itself is not a tissue, but an important cellular component forming a critical compartment of the tissue of the organ.

As described in the Specification, monoclonal antibody 833 reacted with the surface of microvascular endothelium in lung tissue, as assessed by both immunoblotting and tissue immunostaining. A tissue test of lung, heart, brain, liver, kidney, adrenal, testes, intestine, skeletal muscle, and spleen, both Western blotting of whole tissue lysates and subcellular fractions, and immunohistochemical staining of fixed tissue sections, indicated lung specificity, as the antibody reacted with the endothelium only in lung tissue and did not stain the pulmonary artery (indicating specificity for microvasculature over larger blood vessels). The lung epithelial cells, especially obvious in the bronchi, were also nonreactive. The specificity of 833 Mab for the lung vasculature was also quite apparent when the antibody was injected into the tail vein of the rats. Mab 833 also had very low blood counts (> 10-fold less than the control) and very significant tissue uptake in the lung (>50-fold over the control). It was quickly cleared or extracted from the blood by its specific binding to, and transport across, the endothelium of the blood vessel of the lung and not other tissues/organs. Most importantly, mAb 833 appeared specifically to accumulate most rapidly and significantly in the lung with very little detection in other organs. Mass balance analysis showed that a mean of 75±6.4% (833; ranging from 67 to 87%) of the injected dose (10 μg), is targeted to the lung tissue in just 30 minutes.

Mab 833 was found not only to be tissue-specific in its ability to target only lung endothelium, but also caveolae-specific: immunogold EM carried out on ultrathin frozen lung tissue sections showed that Mab 833 associated predominantly with the bulb and neck of the caveolae in microvascular endothelium, and not clathrin-coated pits or epithelial cells (including their caveolae). Larger blood vessel endothelium and controls using heart tissue or nonspecific mouse IgG_1 were negative. Thus, Mab 833 specifically recognizes an antigen that is expressed selectively in caveolae of microvascular endothelium of lung but not other tissues.

The data concerning the conjugate of the drug, dgRA, with the antibody, was presented as a demonstration that the antibody is capable of specifically delivering a drug to a particular tissue. The drug was delivered across the endothelium and only to the underlying cells within the lung tissue; it was not delivered across endothelium to any other organ system. This data clearly demonstrates tissue specificity. It also reveals the caveolae specificity of the representative antibody as well as specific penetration into the lung tissue (but not into other organs) from its specific ability to target the endothelial caveolae of the lung and not other organs. Thus, it is a mischaracterization to state that the effects of targeting the rat lung with mab 833 are "non-specific within lung," as stated by the Examiner. The data described in the specification clearly indicate that tissue-specific delivery of the agent is obtained, because the drug was not delivered to tissue other than lung.

Applicant has clearly demonstrated the contemplated and claimed function, use of an agent that binds to and localizes to a component of caveolae of the luminal surface, to deliver an agent of interest into and across a luminal surface of vascular endothelium in a tissue-specific manner for lung tissue, as described in the specification and as confirmed by the Examiner (see, e.g., the Office Action, made final, at the bottom of page 3). One of ordinary skill in the art, given the teachings of the specification regarding the use of Mab 833 to deliver an agent of interest specifically to lung tissue, would understand that the method is applicable to a wide variety of agents and tissues. The methods need not be limited to treatment of malignancies, as suggested by the Examiner. The methods could also be used to deliver agents for treatment of other diseases of the lung (e.g., asthma, emphysema, tuberculosis, pneumonia, COPH, pulmonary hypertension, cystic fibrosis, and other acquired or genetic lung-related conditions). These diseases should not be considered 'limitations' of the claim, as suggested by the Examiner, but

rather, should be considered to be other representative diseases for which the methods of the invention are useful. One of ordinary skill in the art, given the teachings of the specification, would be able to apply the methods to a wide variety of diseases and tissues.

With regard to the second subheading of the rejection under 35 U.S.C. §112, first paragraph, the Examiner states that the teachings of the specification cannot be extrapolated because "the identification of Mab 833 is an unexpected event." Applicant's Attorney respectfully disagrees with the assertion that the teachings of the Specification cannot be so extrapolated.

The identification of Mab 833 exemplifies the methods that one of ordinary skill in the art can utilize to identify other tissue-specific antibodies. One of ordinary skill in the art, given the teachings of the specification, would understand that the important characteristic of an antibody, or any other agent for use in the methods, is that it binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface. The specification details how to test antibodies or other agents for such specificity. While a certain amount of experimentation may be necessary to identify an antibody or agent having this desired characteristic, there is sufficient evidence in the Specification to guide one of ordinary skill in the art as to how to identify such an antibody or agent. The test for enablement is not solely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). Furthermore, time-consuming experiments are appropriate if the type of experimentation is standard in the art; an extended period of experimentation may be not be undue if the skilled artisan has sufficient direction or guidance. *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Thus, one of ordinary skill in the art, using no more than routine experimentation, would be able to apply the methods of the invention to other antibodies or agents of interest which bind to and localize to components of the caveolae, for tissue-specific targeting of agents.

The Examiner additionally states that "[g]iven the teachings on page 51 and 52 and add to that Applicant's suggested protocols, it is clear that undue experimentation is required to practice the claimed invention" (Office Action, made final, bottom of page 5). The indicated text of the specification, however, does not indicate that undue experimentation is necessary: rather, it indicates that the inventor has achieved a breakthrough that now renders the claimed invention well within the grasp of one of ordinary skill in the art. Pages 51 and 52 indicate that vascular targeting has long been a goal of scientists, but before applicant's invention, it had previously lacked "proof of principle" *in vivo*. Using the methods of the invention, the applicant has for the first time demonstrated successful delivery of agents, by targeting caveolae to overcome the endothelial cell barrier for access to underlying tissue cells. This key discovery, the "proof of principle" long sought, allows one of ordinary skill in the art to achieve delivery of agents of interest, by targeting caveolae in the manner described in the specification and set forth in the claims.

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With regard to the third subheading of the rejection under 35 U.S.C. §112, first paragraph, the Examiner states that "description by function is not sufficient to provide written description for a claimed invention" (Office Action, made final, page 6).

Applicant's Specification provides the relevant features of the agent of interest that are sufficient to distinguish it from other materials. The agent must bind to a component of caveolae of the luminal surface of the vascular endothelium. One of ordinary skill in the art is able to determine what are components of the luminal surface of the vascular endothelium, for example, by using methods such as those described in the specification. Furthermore, the specification provides a significant amount of description regarding the making and identification of a representative agent of interest that binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface, and is tissue specific. One of ordinary skill in the art, given these teachings, would be able to identify similar such agents (e.g., antibodies). The actual antigen need not be identified, nor need the structure of the antigen be described, provided that the antibody have the relevant characteristic (binding to a component of caveolae of the luminal surface of the vascular endothelium, in a tissue-specific manner). This characteristic is sufficient to distinguish the claimed material from other

materials. Given the screening techniques described in the Specification, one of ordinary skill in the art would be able to determine whether an antigen had the relevant characteristic of binding to a component of caveolae of the luminal surface of the vascular endothelium, in a tissue-specific manner. For example, one of ordinary skill in the art could use the methods described in the Examples to determine whether the antigen identified by the antibody is concentrated in caveolae similar to caveolin-1, but unlike the lipid raft marker, 5'nucleotidase (5'NT), using subfractionation of relevant tissue samples. Furthermore, the Specification provides ample detail regarding conjugation of various agents to the antibody and delivery of the agents in a tissue-specific manner. One of ordinary skill in the art, given these teachings, would be able to select an appropriate agent to be delivered in a tissue-specific manner.

In view of these considerations, the subject matter of the claims is sufficiently described in the specification to enable one of ordinary skill in the art to understand what is encompassed by the claims, and to practice the claimed invention without undue experimentation. .

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Doreen M. Hogle, Reg. No. 36,361 for
Elizabeth W. Mata
Registration No. 38,236
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Date: November 18, 2004

APPENDIX

2. A method of delivering an agent of interest into and/or across a luminal surface of vascular endothelium in a tissue-specific manner, comprising the steps of:

a) selecting an agent of interest that binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface, wherein the component to which the agent binds and localizes is tissue specific; and

b) contacting the luminal surface of vasculature with the agent of interest, thereby delivering the agent into and/or across the luminal surface of the vascular endothelium in a tissue-specific manner.

3. A method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner, comprising the steps of:

a) selecting an agent of interest that binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface, wherein the component to which the agent binds and localizes is tissue specific; and

b) contacting the luminal surface of vasculature with the agent of interest, thereby delivering the agent across the luminal surface of the vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner.

4. The method of Claim 3, wherein the agent of interest comprises an active agent component and a transport agent component, wherein the transport agent component binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium.

5. The method of claim 4, wherein the tissue is malignant.

6. The method of claim 4, wherein the agent of interest comprises a nucleic acid.

7. The method of claim 4, wherein the agent of interest comprises an immunotoxin.

8. The method of claim 4, wherein the active agent component is selected from the group consisting of: an antibody, a nucleic acid, a drug, a toxin, and a diagnostic agent.

9. The method of claim 4, wherein the transport agent component binds to and localizes to a molecule present on the luminal surface of a microdomain of the luminal surface of the vascular endothelium.

10. The method of claim 4, wherein the active agent component and the transport agent component are the same component.

11. The method of claim 10, wherein the active agent component is selected from the group consisting of: an antibody, a drug, a toxin, and a diagnostic agent.

12. The method of claim 4, wherein the transport agent component is selected from the group consisting of: an antibody, a peptide, an inactivated virus, a receptor, a ligand and a nucleic acid.

13. The method of claim 12, wherein the transport agent component is an antibody.

14. The method of claim 4, wherein the tissue is selected from the group consisting of: vascular, pulmonary, cardiac, cerebral, nephric, hepatic, endocrinous and intestinal tissue.

15. The method of claim 14, wherein the vascular endothelium of a tissue is vascular endothelium of cardiac tissue, and wherein the agent of interest comprises a selective stimulant.

16. The method of claim 14, wherein the vascular endothelium of a tissue is vascular endothelium of a blood vessel, and wherein the agent of interest comprises an anticoagulant.

17. The method of claim 14, wherein the vascular endothelium of a tissue is vascular endothelium of a blood vessel, and wherein the agent of interest comprises a nucleic acid encoding an anticoagulant.